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Quebec Beer-Drinkers' Cardiomyopathy: Etiological Considerations

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BETWEEN August 1965 and April 1966, a syndrome was encountered in the Quebec City area, with definite clinical, hemodynamic and pathological features. Similar cases were not seen in other parts of the country in spite of a comprehensive search by clinicians and pathologists of major Canadian centres. However, we had the opportunity to examine similar cases in Omaha, Neb., where more than 50 patients were studied and reported by Sullivan and his group.[1] In addition, a similar series of 17 cases was recently described in Belgium by Kesteloot *et al.*[2]

Other cases undoubtedly existed elsewhere, although they may have been reported as idiopathic heart disease[3] or simply not recognized.

The possibility that the Quebec epidemic was viral in origin was considered and 30 patients presenting with cardiomyopathy were studied in this regard. No virus could be isolated. In the serological examinations, the constant feature was the presence of anti-influenza A complement fixing antibody. However, of 59 control alcoholics (who did not present any evidence of cardiomyopathy), 55 showed a positive reaction. Of 68 random control non-alcoholic sera, 51 had a titre equal to or below 1/38.

A similar study conducted at the Institute of Microbiology in Montreal on a control group gave comparable results. There is therefore no decisive argument favouring a viral etiology for this type of cardiomyopathy.

The relationship between alcoholism and heart disease has been recognized for more than 100 years. For instance, Bollinger[4] felt that the heavy beer drinking occurring in Munich 80 years ago was responsible for cardiac dilatation. However, he also believed that "apoplexy" and "nephritis" were secondary to the "plethora" induced by beer consumption.

There is a certain similarity between the Quebec beer-drinkers' cardiomyopathy and beriberi heart disease—the manner of death in our patients was similar to that described in Shöshin beriberi.[5] However, a high cardiac output is expected in the acute stage of this heart disease.[6] We do not think that chronic beriberi heart disease, hypokinetic and unresponsive to thiamine, is a common entity;[7] the presence of abnormal erythrocyte transketolase* activity found in these patients may simply reflect recent nutritional deficiency secondary to heart failure.[8]

Evans[9] has stressed the frequency of various types of arrhythmias and of abnormal electrocardiograms in alcoholics; this does not apply to the cases under study.

Most published series of chronic idiopathic cardiomyopathies have a high proportion of alcoholics (about 60%),[10] and it is generally believed that excessive alcohol ingestion can lead to myocardial degeneration and fibrosis,[11] especially as alcohol has been shown to have a deleterious effect on myocardial function.[12] Concerning this diagnostic possibility, it should be stressed that 16 of the 22 Quebec patients, seen at follow-up during February and March, 1967, had returned to their drinking habits, consuming as much of the same brand of beer as before. Their food habits were identical. Many of them were inebriated when seen at follow-up. In spite of this, none had symptoms or physical signs referable to their cardiovascular system. Chest films were all within normal limits. Hemodynamic studies of three patients in this group, a year after the acute illness, showed normal myocardial function but the expected impairment of myocardial reserve in the face of marked and regular alcohol ingestion up to the day preceding the hemodynamic studies. In July 1967, a patient in this series (B-15) died of carcinoma of the larynx. He had been drinking beer regularly during the past year and was free of symptoms or signs referable to the cardiovascular system. At autopsy, the heart was macroscopically normal (350 g.). On light microscopy, there was patchy interstitial fibrosis throughout the myocardium. There were no degenerative changes of the type described during the acute stage of the disease in the myocardial fibres. It would therefore appear that the myocardial degeneration under study occurred as a sudden episode, limited in time and space, in the alcoholic "career" of 48 patients and that alcohol was not the sole etiological agent involved in the genesis of this syndrome.

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*Transketolase—enzyme in the phosphogluconate oxidative pathway.

A parallel can be drawn between this episode and the 2000 cases of "beer" poisoning which occured in Manchester in 1900.[13] A Royal Commission, after an open and thorough investigation, came to the conclusion that this syndrome was due to the contamination of beer by arsenic.[14] Certain aspects of the Manchester beer drinkers' disease are remarkable: (1) the "unusual amount of heart failure and edema"[15] as compared to that in the average non-alcoholic case of arsenic intoxication; (2) the "peculiar idiosyncrasy which people seemed to have",[16] in that many similarly exposed heavy beer drinkers were symptom-free; (3) the "amount of arsenic found in the beer and actually consumed [daily] by the patient was . . . not sufficient to explain the poisoning";[17] (4) eminent physicians, such as Sir William Gowers,[18] pointed out that they prescribed 10 times this amount of arsenic to epileptics for long periods of time without side effects; (5) it was therefore concluded that "the alcoholic vehicle in the form of beer accentuated the toxic effect of arsenic".[19]

The similarities between the Manchester and Quebec episodes led us to investigate the constituents of the beer itself. All surviving patients and those who could be questioned, drank preferably (but not exclusively) brand XXX. The XXX brewery is in an unusual position in Quebec City, having been established on the site of the oldest brewery in North America built by Jean Talon in 1668 to help combat alcoholism amongst French settlers. Its excellent tasting brew was (and still is) very popular in Quebec and accounts for approximately 80% of the local market. A beer of the same name is manufactured in Montreal and, as far as could be ascertained, the only difference in both products at that time was that the Quebec XXX Brand beer contained approximately 10 times more cobalt sulphate. This chemical had been added to some Canadian beers since July 1965 to improve the stability of the foam. The absence of satisfactory foam in spite of adequate carbon dioxide content has been a recent problem and is due to the washing of glasses in taverns with detergents and to insufficient rinsing with plain water. For this reason, in larger breweries, cobalt sulphate has been added only to draught beer. However, in smaller breweries, such as in Quebec City, separate batches were not brewed for bottle and for draught beer, and cobalt sulphate was therefore added to all the beer processed in the XXX brewery. Thus, the intake of this additive was increased to much higher levels than in Montreal.

In both Quebec City and Omaha (Fig. 1), the syndrome appeared a month after the addition of cobalt sulphate to beer and no new cases developed one month after this procedure was discontinued.[20] A similar relationship between cobalt addition and the syndrome was found in Belgium.[21] It has been impossible to obtain from government sources or from the industry the cobalt content of locally brewed beers in North America, and it is possible that other series may go undetected.

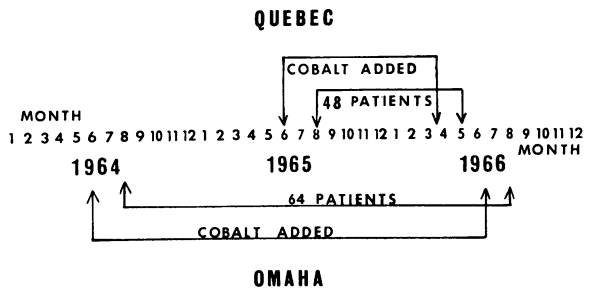

Fig. 1

Cobalt has been used extensively as an antianemic agent and it is remarkable that the Louvain, Omaha and Quebec patients were polycythemic. Elsewhere in this issue, Bonenfant and his co-workers[22] have in the Quebec series described thyroid lesions typical of the cobalt-induced goitres.

As in the Manchester episode, the fact that cobalt has in the past been prescribed in much higher dosage—24 pints of brand XXX beer would contain approximately 8 mg. of cobalt sulphate, while four tablets of Roncovite* (cobalt chloride, 15 mg. and ferrous sulfate 100 mg.) would represent a daily intake of 60 mg. of cobalt chloride—without producing such a devastating effect would tend to indicate that other factors have increased these patients' susceptibility to cobalt.

The absorption of cobalt is known to be extremely variable: (a) it is diminished after a meal;[23] (b) it varies with the quantity and type of dietary protein;[24] (c) it varies with the pH of the stomach and upper duodenum;[23] (d) it is increased if iron deficiency exists.[25]

Cobalt has been shown to have a biological action of great complexity. It has been shown *in vitro* to stimulate certain enzymatic systems[26, 27] and inhibit others.[28] Webb and his co-workers, in a series of papers,[29-32] have thoroughly investigated the biological action of cobalt and have demonstrated that the inhibition of ketoacid oxidation is the point at which cobalt acts on cell metabolism. The metal forms a chelate with the dithiol form of lipoic acid,

*Hoescht.

a co-enzyme of ketoacid dehydrogenation, thus blocking the Krebs cycle and aerobic cellular respiration.

The type of biological activity of cobalt is dependent on the concentration of the metal. For instance it has been shown[33] that there is a very narrow critical range of dosage which is high enough to block iodine uptake and not so high as to block hyperplasia induced by thyroid-stimulating hormone. Finally, the action of cobalt on various systems, *in vitro*[32] and *in vivo*,[34] will be modified by the presence of certain amino acids such as methionine and cysteine: it is believed that these sulfhydryl-containing amino acids form an inert complex with cobalt.

It can be seen that a number of independent variables will alter the nature and the magnitude of the biological action of cobalt. Which of these variable factors was responsible for the clinical condition seen in Quebec City beer drinkers is not known at the present, and is a problem that may be solved only by further research.

The myocardial toxicity of cobalt has been well studied; ^{58}cobalt when administered is deposited in the myocardium.[35] The metal will diminish the contractility of isolated guinea-pig's papillary muscle[36] and has a deleterious effect on myocardial function in the rabbit[37] and guinea-pig.[38] Heraut[39] has found in various species diffuse myocardial degeneration with interstitial edema as the result of cobalt. In addition, a common finding was that of pericardial effusion, a feature which impressed clinicians in Louvain, Omaha and Quebec and has not been reported in association with other types of alcoholic cardiomyopathy.[40]

It would appear, therefore, that cobalt was the essential factor in the production of the Quebec beer-drinkers' cardiomyopathy.

The chelating agent ethylenediaminetetra-acetic acid (EDTA) has been shown to prevent cobalt intoxication in the animal.[39, 41] Had this metal been known to be present in beer at the time of the epidemic, the prompt administration of EDTA might have saved some of our patients. The clinician accustomed to knowing the exact composition of the drugs he uses will therefore seriously question the necessity for the secrecy that surrounds the use of food or drink additives.

Summary Quebec beer-drinkers' cardiomyopathy is felt to be multicausal in origin. While it is probable that excessive alcohol ingestion and various nutritional deficiencies played an important part, it is believed that the addition of cobalt to beer was the essential factor in the production of this type of cardiomyopathy.

Résumé La cardiomyopathie des buveurs de bière québecois est multicausale. A l'éthylisme et au déséquilibre nutritionnel, s'ajoute, comme facteur essentiel, l'addition de cobalt à la bière.

REFERENCES

1. MCDERMOTT, P. H. *et al.*: *J. A. M. A.*, **198**: 253, 1966.
2. KESTELOOT, H. *et al.*: *Acta Cardiol. (Brux.)*, **21**: 341, 1966.
3. ALEXANDER, C. S.: *Amer. J. Med.*, **41**: 213, 1966.
4. BOLLINGER, O.: *Deutsch. Med. Wschr.*, **10**: 180, 1884.
5. DE LANGEN, C. D. AND LECHTENSEIN, A.: A clinical text book of tropical medicine, Amsterdam, 1936.
6. LESSARD, R., BERNIER, J. P. AND MORIN, Y.: *Canad. Med. Ass. J.*, **80**: 112, 1959.
7. BRINK, A. J., LOCHNER, A. AND LEWIS, C. M.: *S. Afr. Med. J.*, **40**: 581, 1966.
8. HARO, E. N., BRIN, M. AND FALOON, W. W.: *Arch. Intern Med. (Chicago)*, **117**: 175, 1966.
9. EVANS, W.: *Amer. Heart J.*, **61**: 556, 1961.
10. MASSUMI, R. A. *et al.*: *Circulation*, **31**: 19, 1965.
11. DYE, C. L. *et al.*: *Ann. Intern. Med.*, **58**: 426, 1963.
12. FERRANS, V. J.: *Amer. J. Med. Sci.*, **252**: 89, 1966.
13. REGAN, T. J. *et al.*: *Trans. Ass. Amer. Physicians*, **78**: 282, 1965.
14. REYNOLDS, E. S.: *Lancet*, **1**: 166, 1901.
15. Annotation: *Ibid.*, **2**: 218, 1901.
16. Royal Commission on Arsenical Poisoning: *Ibid.*, **1**: 672, 1901.
17. TUNNICLIFFE, F. W. AND ROSENHEIM, O.: *Ibid.*, **1**: 318, 1901.
18. GOWERS, W. R.: *Ibid.*, **1**: 98, 1901.
19. KELYNACK, T. N.: *Ibid.*, **1**: 472, 1901.
20. SULLIVAN, J. F.: *Ann. N.Y. Acad. Sci.*, In press.
21. KESTELOOT, H.: Personal communication.
22. KLINCK, G. H.: *J. A. M. A.*, **158**: 1347, 1955.
23. PALEY, K. R. AND SUSSMAN, E. S.: *Metabolism*, **12**: 975, 1963.
24. JONES, H. D. J. AND PERKINS, D. J.: *Biochim. Biophys. Acta*, **100**: 122, 1965.
25. POLLACK, S. *et al.*: *J. Clin. Invest.*, **44**: 1470, 1965.
26. BABINET, C. *et al.*: *Biochem. Biophys. Res. Commun.*, **19**: 95, 1965.
27. WILLIAMS, V. R. AND SELBIN, J.: *J. Biol. Chem.*, **239**: 1635, 1964.
28. LEVY, H., LEVISON, V. AND SCHADE, A. L.: *Arch. Biochem.*, **27**: 34, 1950.
29. DANIEL, M. *et al.*: *Brit. J. Exp. Path.*, **44**: 163, 1963.
30. DINGLE, J. T. *et al.*: *Biochim. Biophys. Acta*, **65**: 34, 1962.
31. WEBB, M.: *Ibid.*, **65**: 47, 1962.
32. *Idem*: *Ibid.*, **89**: 431, 1964.
33. KRISS, J. P. *et al.*: *Endocrinology*, **59**: 555, 1956.
34. ORTEN, J. M. AND BUCCIERO, M. C.: *J. Biol. Chem.*, **176**: 961, 1948.
35. BLANQUET, P. *et al.*: *Arch. Mal. Prof.*, **26**: 235, 1965.
36. KAUFMANN, R. AND FLECKENSTEIN, A.: *Pflueger Arch. Ges. Physiol.*, **282**: 290, 1965.
37. JALAVISTO, E. *et al.*: *Ann. Acad. Sci. Fenn. (Med.)*, **115**: 1, 1965.
38. LAMARCH, M. AND EST, M.: *C. R. Soc. Biol. (Paris)*, **154**: 187, 1960.
39. HERAUT, L. A.: Etude clinique et expérimentale de la toxicité du cobalt, Delmas, Paris, 1962.
40. Case Records of the Massachusetts General Hospital, Weekly Clinicopathological Exercises, Case 45-1966: *New Eng. J. Med.*, **275**: 835, 1966.
41. NOFRE, C., CLEMENT, J. M. AND CIER, A.: *Path. Biol. (Paris)*, **11**: 853, 1963.